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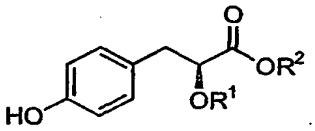
(54) Title: AN IMPROVED PROCESS FOR THE PREPARATION OF 3-ARYL-2-HYDROXY PROPANOIC ACID DERIVATIVES

(57) Abstract: The present invention relates to an improved process for the preparation of 3-aryl-2-hydroxy propanoic acid derivatives of the formula (1) where R1 represents hydrogen atom or (C1-C6)alkyl group and R2 represents (C1-C6)alkyl group which comprises: (i) selectively benzylating L-tyrosine to yield compound of the formula (15), (ii). diazotising the compound of the formula (15) to produce compound of formula (8), (iii) simultaneous etherification and esterification of compound of formula (8) to obtain crude compound of formula (9) with ee>90 %, (iv) hydrolysing the crude compound of formula (9) to produce compound of formula (9a) acid, (v) treating the compound of formula (9a) with chiral base to produce pure salt of formula (16), (vi) converting the compound of formula (16) to pure compound of formula (9a), (vii) esterifying pure compound of formula (9a) to produce pure compound of formula (9) (viii) debenzylating the compound of formula (9) to yield pure compound of formula (1).

AN IMPROVED PROCESS FOR THE PREPARATION OF 3-ARYL-2-HYDROXY PROPANOIC ACID DERIVATIVES

Field of the invention

The present invention relates to an improved process for the preparation of 3-aryl-2-hydroxy propanoic acid derivatives of the formula (1)



(1)

wherein R^1 represents hydrogen atom or $(C_1\text{-}C_6)$alkyl group and R^2 represents $(C_1\text{-}C_6)$alkyl group.

The compound of formula (1) is useful as an intermediate for the preparation of many pharmaceutically active compounds.

Background of invention

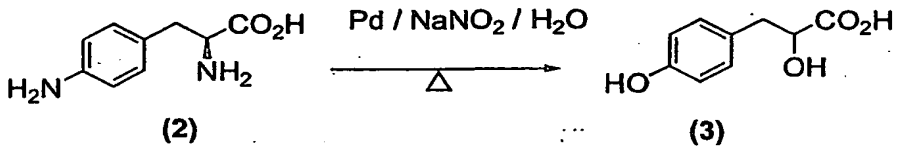
The process for the preparation of 3-aryl-2-hydroxy propanoic acid, its derivatives and analogs exhibiting various pharmacological actives have been described in US 5,232,945, US 5,306,726, WO 91/11999, DE 1,948,373, DE. 2,033,959, DE 2,014,479, DE 1,668,938, WO 91/19702, WO 92/0252, WO 96/04260, WO 96/0426, WO 95/17394. In addition, these compounds are considered to be useful for treating certain eating disorders, in particular the regulation of appetite and food intake in subjects suffering from disorders associated with eating such as anorexia nervosa and disorders associated with overeating such as obesity and anorexia bulimia.

3-Aryl-2-hydroxy propanoic acid derivatives are also used as sweetening agent (Gries et.al. EP 55,689 (1982)), also in photosensitive materials (Komamura et.al. JP 6022850) and also in liquid crystals (Grey et.al. WO 88/02390).

It is also a part of sesquiterpene lactone glycoside isolated from Crepis tectorium (Kisiel Wanda et.al. Phytochemistry, 2403, 28 (9) (1989)]. It is also part of Aeruginorins 102A and B, a new class of Thrombin inhibitors from the Cyanobacterium Microcystis vindis.

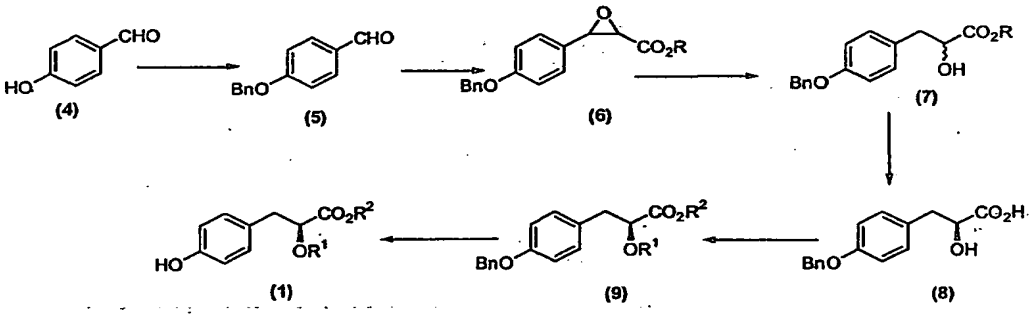
3-Aryl-2-hydroxy propanoic acid is prepared by several methods reported in the literature.

Hisashi Matruda, et.al., Tet. 52 (46) 14501 (1996)



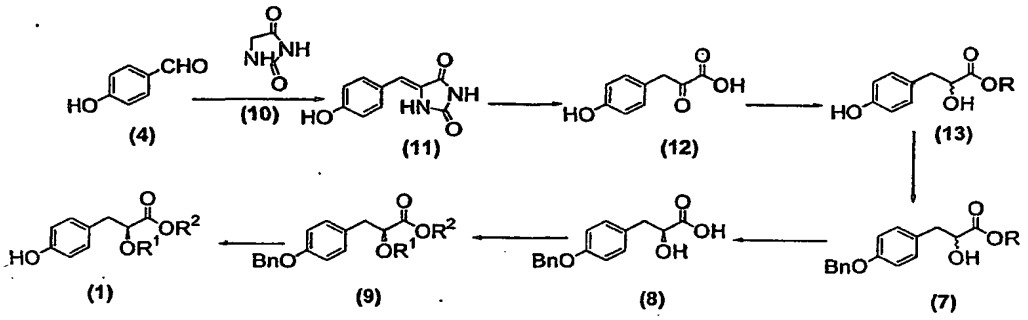
Scheme-1

In our WO publication No. 00/26200 we have described process for preparing the compound of formula (1). The reaction schemes are shown below :



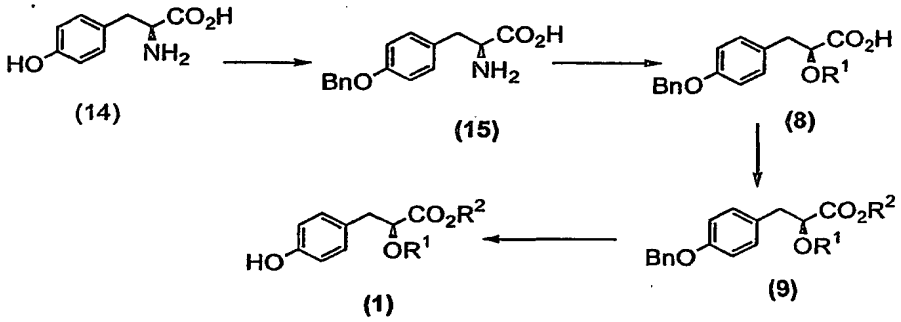
Scheme-2

Though it is convergent synthetic method, the compound of formula (7) is produced in racemic mixture, which has to be resolved to get the optically pure material.



Scheme-3

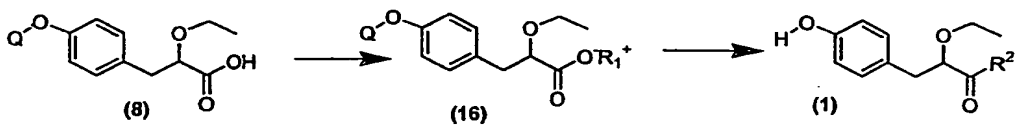
In this process too the resolution has to be carried out for compound of formula (7).



Scheme-4

WO 99/62872 and WO01/40159 describes a process for the preparation of compound of formula (I), wherein R^2 is OH or the group OR^P, where in R^P is protecting group consisting of H, benzyl or (C_1-C_3)alkyl,which comprises reacting a racemic compound of the formula II where Q is a protecting group or H, with a chiral amine forming a salt of the formula III, subsequently separating the diastereomers by crystallization followed by removal of the amine and deprotecting the Q group of the resulting compound with a deprotecting agents and optionally protecting a free carboxylic acid function with the group R^P.

The reaction is shown in scheme 5 below :



Scheme-5

Objective of present invention

The main objective of the present invention is to provide a simple and robust process for the preparation of the compound of formula (1) with high chemical and chiral purity.

Another objective of the present invention is to produce pure and stable compound of formula (9) acid salt with respect to chemical and chiral purities.

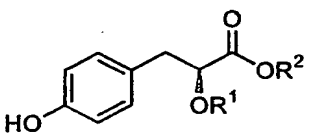
To convert the crude compound of formula (9) (partially racemised) to compound of formula (9) acid and to get pure compound of formula (9) acid, which is back esterified to get pure compound of formula (9).

To overcome the problem of partial racemisation during the conversion of compound of formula (8) to compound of formula (9).

To avoid use of highly reactive, difficult to handle and expensive chemicals such as sodium hydride and ethyl iodide and replaced with simple, inexpensive chemicals such as diethylsulphate and potassium carbonate.

Detailed description of the invention

Accordingly, the present invention provides an improved process for the preparation 3-aryl-2-hydroxy propanoic acid derivatives of the formula (1)



(1)

wherein R^1 represents hydrogen atom or (C_1-C_6)alkyl group such as methyl, ethyl, propyl, isopropyl, n-butyl, t-butyl and the like, and R^2 represents (C_1-

C_6)alkyl group such as methyl, ethyl, propyl, isopropyl and the like which comprises:

(i). selectively benzylating L-tyrosine of the formula (14) using benzyl halide, $CuSO_4$ and sodium hydroxide in a solvent to yield a compound of the formula (15),

(ii). diazotising the compound of the formula (15) using diazotizing agent in the presence of an acidic reagent and an organic solvent to produce compound of the formula (8a),

(iii). simultaneous etherification and esterification of compound of formula (8a) using alkylating agent in the presence of a base and a solvent to obtain crude compound of formula (9) with ee >90 % wherein R^1 represents hydrogen or lower alkyl group and R^2 represents lower alkyl group,

(iv). hydrolysing the crude compound of formula (9) obtained in step (iii) above in polar solvents using aqueous alkali to produce compound of formula (9a) acid wherein R^1 represents hydrogen or lower alkyl group,

(v). treating the compound of formula (9a) acid where R^1 represents hydrogen and lower alkyl group with chiral base in the presence of solvent to produce chemical and chiral pure (ee >99 %) salt of formula (16) where R^1 represents hydrogen or lower alkyl group and X represents chiral bases such as R(+)-α-methylbenzylamine, S(+) phenylglycinol, cinchonidine, ephidrine, N-octylglucaramine, N-methylglucaramine and the like,

(vi). if desired, recrystallizing the compound of formula (16) obtained above in a solvent to produce highly pure compound of formula (16) where R^1 represents hydrogen or lower alkyl group,

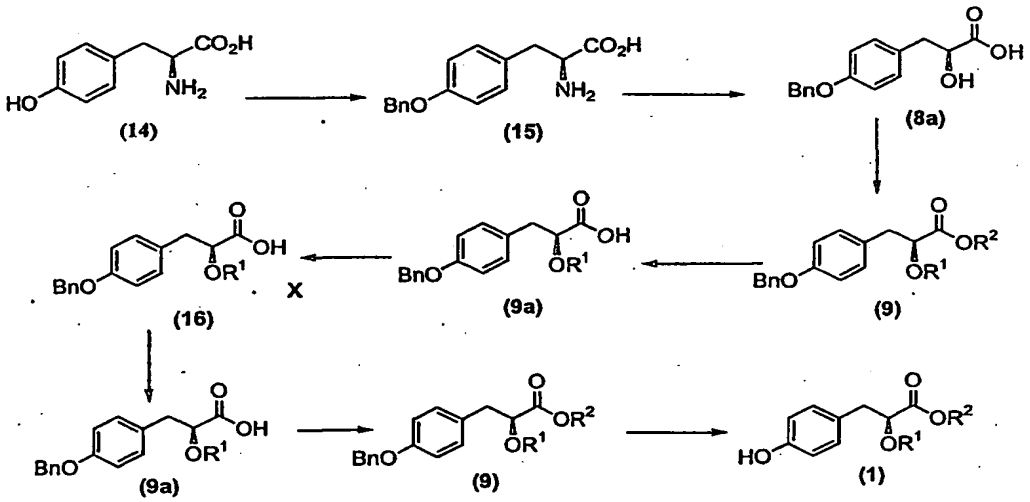
(vii). converting the compound of formula (16) defined above using a solvent and an acid to pure compound of formula (9a) where R^1 represents hydrogen or lower alkyl group,

(viii). esterifying the pure compound of formula (9a) defined above using alkylating agent in the presence of base or acid or acidic resin to produce pure

compound of formula (9) where R^1 represents hydrogen or lower alkyl group and R^2 represents lower alkyl group and

(ix). debenzylating the compound of formula (9) using solvents in the presence of metal catalysts to yield pure compound of formula (1) where R^1 represents hydrogen or lower alkyl group and R^2 represents lower alkyl group.

The process explained above is shown in scheme-6 below :



Scheme-6

The process of the present invention starts with benzylating the compound formula (14) using benzyl halide such as benzyl chloride, benzyl bromide and the like, $CuSO_4$, sodium hydroxide in the presence of solvents such as aqueous methanol, ethanol and the like to afford compound of the formula (15). Diazotization of the compound of the formula (15) using diazotizing agent such as sodium nitrite, isoamyl nitrite, potassium nitrite, ammonium nitrite and the like under acidic conditions using acids such as sulfuric acid, HCl, acetic acid and the like, in an organic solvent such as $CHCl_3$, 1,4-dioxane, THF, acetone and the like, gives the compound of the formula (8a). Simultaneous etherification and esterification of compound of formula (8a) to obtain crude compound of formula (9) may be carried out using alkyl sulfates

such as diethyl sulphate, dimethylsulphate and the like or alkyl halides such as ethyl iodide, methyliodide and the like, in the presence of solvents such as hydrocarbons like toluene, benzene and the like or DMF, DMSO, methyl isobutyl ketone (MIBK) and the like, in alkali bases such as sodium carbonate, potassium carbonate, sodium methoxide, sodium hydride and the like. Alternatively, the compound of formula (9) may also be prepared by slow addition of compound of formula (8a) to a solution of DMF, sodium hydride, and alkali halides such as methyl iodide, ethyl iodide and the like at a temperature ranging from 0 to 80 °C. The compound of formula (9) upon hydrolysis in polar solvents like alcohols such as methanol, ethanol, propanol, isopropanol and the like or ketonic solvents such as acetone, methyl ethyl ketone and the like using aqueous alkali base such as sodium hydroxide or potassium hydroxide yields compound of formula (9a). The resolution of compound of formula (9a) with chiral base such as R(+)-α-methylbenzylamine, S(+) phenylglycinol, cinchonidine, ephidrine, N-octylglucaramine, N-methylglucaramine and the like using solvents such as alkyl ester such as methyl acetate, ethyl acetate, ethyl propanoate, n-butylacetate and the like or alcohol such as methanol, ethanol, propanol, isopropanol and the like or ketone such as acetone, methyl isobutyl ketone and the like or acetonitrile produces the chemical and chiral pure compound of formula (16) where X represents chiral base such as R(+)-α-methylbenzylamine, S(+) phenylglycinol, cinchonidine, ephidrin, N-octylglucaramine, N-methylglucaramine and the like. The compound of formula (16) defined above may further purified by recrystallization from solvents such as alkyl ester such as methyl acetate, ethyl acetate, ethyl propanoate, n-butylacetate and the like or alcohol such as methanol, ethanol, propanol, isopropanol and the like or ketone such as acetone, methyl ethyl ketone, methyl isobutyl ketone and the like or acetonitrile to obtain highly pure compound of formula (16). The pure compound of formula (9a) is

obtained from the compound of formula (16) by treating with acid such as hydrochloric acid, sulfuric acid and the like in the presence of solvent such as toluene, xylene, ethyl acetate, diethyl ether, methyl tertiary butyl ether and the like. The pure compound of formula (9a) obtained above is esterified with suitable alcohols such as methanol, ethanol, propanol, isopropanol, butanol and the like or alkyl sulfates such as methyl sulfate, ethyl sulfate and the like in the presence of acids such as hydrochloric acid, sulfuric acid and the like or acidic resins such as amberlite, amberlist and the like or bases such as potassium carbonate, sodium carbonate, sodium bicarbonate, potassium bicarbonate or organic bases such as alkoxides like sodium ethoxide, potassium tertiary butoxide or triethyl amine and the like to produce pure compound of formula (9). The debenzylation of the compound of formula (9) using THF, aqueous acetic acid, ethyl acetate, aqueous or non aqueous (C_1-C_6) alcohols such as methanol, ethanol, propanol, isopropanol and the like in the presence of metal catalysts such as Pd/C produces pure compound of formula (1).

It is appreciated that in any of the above mentioned reactions, any reactive group in the substrate molecule may be protected according to conventional chemical practice. Suitable protecting groups in any of the above mentioned reactions are tertiarybutyl dimethyl silylchloride, methoxymethyl chloride and the like. The methods of formation and removal of such protecting groups are those conventional methods appropriate to the molecule being protected.

The invention is described in the examples given below which are provided by way of illustration only and therefore should not construed to limit the scope of the invention.

Example 1

Step (i)

Preparation of (S)-2-amino-3-(4-benzyloxyphenyl)propanoic acid of the formula (15)

To a solution of L-tyrosine of the formula (14) (250 g) in 2N NaOH solution (552 ml), copper sulphate solution (172 g of $CuSO_4$ in 600 ml of water) was added and heated at 60 °C for 2 h. The reaction mixture was cooled to room temperature and methanol (2.5 L) and 2N NaOH (83 ml) was added and then benzyl chloride (15 ml) was added drop wise. The reaction mass was allowed to warm to room temperature. The precipitate was filtered and washed to give the title compound as white to off-white solid (260 g, 70 %) (*Ref. The practice of peptide synthesis, M. Bodanszky & A. Bodanszky pp50*).

Step (ii)

Preparation of S(-)-2-hydroxy-3-(4-benzyloxyphenyl)propanoic acid of the formula (8a)

To a stirred solution of (S)-2-amino-3-(4-benzyloxyphenyl)propanoic acid of the formula (15) (300 g) obtained in step (i) above, in acetone (1.8 L) and dilute H_2SO_4 (75 ml in 1.2 L of H_2O) at 0 °C, a solution of $NaNO_2$ (210 g in 400 ml H_2O) was added slowly between 0 °C to 15 °C. After complete addition of $NaNO_2$ the reaction mixture was maintained below 25 °C for a period of 3 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was extracted with ethyl acetate. The organic extracts were concentrated and the residue was purified by washing with diisopropyl ether to give the title compound of the formula (8a) as off white to yellowish solid (159 g, 52.8 %).

Step (iii)

Preparation of crude S(-) ethyl 2-ethoxy-3-(4-benzyloxyphenyl)propanoate of the formula (9)

A mixture of S(-)-2-hydroxy-3-(4-benzyloxyphenyl)propanoic acid of the formula (8a) (50 g), potassium carbonate (152 g), diethyl sulfate (113 g), and toluene (750 ml) was taken in a round bottom flask and refluxed for 24 to 36 h. The completion of the reaction was monitored by TLC. After completion of the reaction, water (500 ml) was added and stirred to dissolve inorganic salts. The organic layer was concentrated to yield crude ethyl 2-ethoxy-3-(4-benzyloxyphenyl)propanoate of the formula (9) (56 g, 93 %).

The other compounds of formula (9) are also prepared using the solvents given below following the procedure as described above :

Example No.	R^1 and R^2	Reagent	Solvent	Yield
1	Methyl	DMS	Toluene / K_2CO_3	86 %
2	Methyl	DMS	DMF	76 %
3	Methyl	NaH / CH_3I	DMF	90 %
4	Ethyl	DES	DMF	76 %
5	Ethyl	NaH / C_2H_5I	DMF	97 %

Step (iv)

Preparation of S(-) 2-ethoxy-3-(4-benzyloxyphenyl)propanoic acid the formula (9a)

To a solution of crude S(-) ethyl 2-ethoxy-3-(4-benzyloxyphenyl)propanoate (180 g) of the formula (9) obtained in step (iii), in methanol (900 ml) cooled to 10-20 °C, sodium hydroxide solution (900 ml) was added slowly. The reaction temperature was raised to 25-30 °C and stirred for 4-6 h. Completion of the reaction was monitored by TLC. After completion of the reaction, water (900 ml) was added and extracted with toluene (2 X 900 ml) to remove impurities. Aqueous layer was removed and pH was adjusted to 2 and extracted with

toluene (2 X 900 ml). Combined organic layers were washed with water and concentrated to afford the title compound of the formula (9a) (139 g, 84 %).

Step (v)

Preparation of (S)-2-ethoxy-3-(4-benzyloxyphenyl)propanoic acid α–methyl benzyl amine salt of the formula (16)

To S(-) 2-ethoxy-3-(4-benzyloxyphenyl)propanoic acid (141 g) the formula (9a) dissolved in ethylacetate (1.4 L), R(+)-α-methylbenzylamine (57 g) was added slowly and stirred for 3-4 h. The precipitated white solid was filtered (recrystallised from ethylacetate 1.5 L if required, to the desired purity) to yield pure (S)-2-ethoxy-3-(4-benzyloxyphenyl)propanoic acid α–methyl benzyl amine salt of the formula (16) (125g, 63 %).

The other compounds of formula (16) are also prepared from S(-) 2-ethoxy-3-(4-benzyloxyphenyl)propanoic acid or S(-) 2-methoxy-3-(4-benzyloxyphenyl)propanoic acid using the chiral bases and solvents given below following the procedure as described above :

Example No.	R^1	Chiral base	Solvent	Yield
1	Ethyl	R(+)-α-methylbenzylamine	Acetone	77 %
2	Ethyl	R(+)-α-methylbenzylamine	Isopropyl alcohol	74 %
3	Ethyl	R(+)-α-methylbenzylamine	acetonitrile	85 %
4	Ethyl	R(+)-α-methylbenzylamine	n-butyl acetate	81.5 %

5	Ethyl	R(+)-α-methylbenzylamine	Methyl isobutyl ketone	74 %
6	Ethyl	phenyl glycinol	Ethyl acetate	70 %
7	Ethyl	phenyl glycinol	Acetone	56 %
8	Ethyl	phenyl glycinol	Isopropyl alcohol	60 %
9	Ethyl	phenyl glycinol	acetonitrile	62 %
10	Ethyl	phenyl glycinol	n-butyl acetate	68 %
11	Ethyl	phenyl glycinol	Methyl isobutyl ketone	59 %
12	Methyl	R(+)-α-methylbenzylamine	Acetone	75 %
13	Methyl	R(+)-α-methylbenzylamine	Isopropyl alcohol	72 %
14	Methyl	R(+)-α-methylbenzylamine	Ethyl acetate	60 %
15	Methyl	phenyl glycinol	Acetone	55 %
16	Methyl	phenyl glycinol	Isopropyl alcohol	62 %
17	Methyl	phenyl glycinol	Ethyl acetate	66 %

Step (vi)

Preparation of (S)-methyl 2-ethoxy-3-(4-benzyloxyphenyl)propanoate of the formula (9)

A mixture of (S)-2-ethoxy-3-(4-benzyloxyphenyl)propanoic acid α–methyl benzyl amine salt of the formula (16) or (S)-2-ethoxy-3-(4-benzyloxyphenyl)propanoic acid phenyl glycinol salt of the formula (16), (6.7 g) water (70 ml) and toluene (35 ml) was taken in a reaction flask and stirred for 5-10 min. The reaction mass was cooled to 10-15 °C and 25% cold sulfuric acid was added slowly to adjust pH of the reaction mass to 2. Aqueous and

organic layers were separated. Aqueous layer was extracted with toluene (35 ml). The combined toluene layers were washed with water (20 ml) and evaporated to yield (S) 2-ethoxy-3-(4-benzyloxyphenyl)propanoic acid the formula (9a) (4 g).

The pure compound of formula (9a) obtained above was dissolved in methanol (35 ml), sulfuric acid (0.4 ml) was added and stirred at refluxing temperature for 12-24 h. Completion of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was cooled to room temperature, diluted with water (35 ml) and extracted with toluene (2 X 35 ml). The combined organic layers were washed with 0.5 % sodium hydroxide solution (30 ml) and water (50 ml) and concentrated to afford pure tile compound of the formula (9) (3.5 g, 83 %).

The other compounds of formula (9) from compounds of formula (9a) are also prepared using the solvents given below following the procedure as described above :

Example No.	R^1	R^2	Solvent	Yield
1	Ethyl	Ethyl	Ethanol / H_2SO_4	81 %
2	Ethyl	Ethyl	DES / K_2CO_3	80 %
3	Ethyl	Methyl	DMS / K_2CO_3	78 %
4	Ethyl	Isopropyl	Isopropyl alcohol / H_2SO_4	84 %
5	Methyl	Ethyl	Ethanol / H_2SO_4	80 %
6	Methyl	Ethyl	DES / K_2CO_3	76 %
7	Methyl	Methyl	DMS / K_2CO_3	74 %
8	Methyl	Isopropyl	Isopropyl alcohol / H_2SO_4	82 %
9	Methyl	Methyl	Methanol / H_2SO_4	85 %

Step (vii)

Preparation of (S)-methyl 2-ethoxy-3-(4-hydroxyphenyl)propanoate of the formula (1)

A mixture of (S)-methyl 2-ethoxy-3-(4-benzyloxyphenyl)propanoate of the formula (9) (56 g) in aqueous methanol (300 ml) and slurry of 5% palladium carbon (6 g in 60 ml water) was taken in hydrogenation flask and hydrogenated on Parr shake flask at 60 psi pressure for 6-8 h at room temperature. Completion of the reaction was monitored by TLC. After completion of the reaction, the catalyst was filtered and the filtrate was evaporated to yield tile compound of the formula (1) (39 g, 96 %).

The other compounds of formula (1) are also prepared using the solvents given below following the procedure as described above:

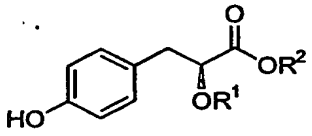
Example No.	R^1	R^2	Solvent	Yield
1	Ethyl	Isopropyl	Aqueous methanol	87 %
2	Ethyl	Isopropyl	Aqueous ethanol	85 %
3	Ethyl	Isopropyl	Aqueous isopropyl alcohol	92 %
4	Ethyl	Isopropyl	Aqueous acetic acid	80 %
5	Ethyl	Ethyl	Aqueous methanol	96 %
6	Ethyl	Ethyl	Aqueous ethanol	82 %
7	Ethyl	Ethyl	Aqueous isopropyl alcohol	89 %
8	Ethyl	Ethyl	Aqueous acetic acid	86 %
9	Methyl	Isopropyl	Aqueous methanol	92 %
10	Methyl	Isopropyl	Aqueous ethanol	84 %
11	Methyl	Isopropyl	Aqueous isopropyl alcohol	90 %
12	Methyl	Isopropyl	Aqueous acetic acid	88 %

Advantages of the present process

- An efficient synthesis for the production of compounds of formula (I) with high chiral and chemical purity.
- The overall yield of the process has been improved.
- Pyrophoirc and exotic reagents like NaH are replaced with simple, inexpensive chemicals such as diethylsulphate and potassium carbonate.

Claims :

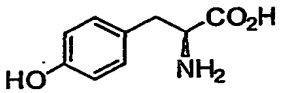
1. An improved process for the preparation 3-aryl-2-hydroxy propanoic acid derivatives of the formula (1)



(1)

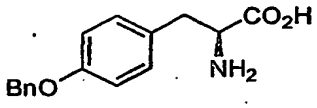
where R^1 represents hydrogen atom or $(C_1\text{-}C_6)$alkyl group and R^2 represents $(C_1\text{-}C_6)$alkyl group which comprises:

(i). selectively benzylating L-tyrosine of the formula (14)



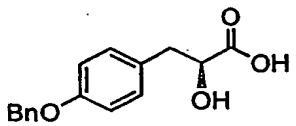
(14)

using benzyl halide, $CuSO_4$ and sodium hydroxide in a solvent to yield a compound of the formula (15),



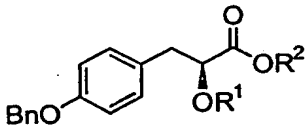
(15)

(ii). diazotising the compound of the formula (15) using diazotizing agent in the presence of an acidic reagent and an organic solvent to produce compound of the formula (8a),



(8a)

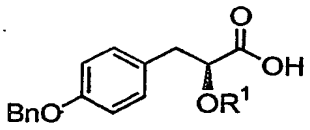
(iii). simultaneous etherification and esterification of compound of formula (8a) using alkylating agent in the presence of a base and a solvent to obtain crude compound of formula (9) with ee >90 %



(9)

wherein R^1 represents hydrogen or lower alkyl group and R^2 represents lower alkyl group,

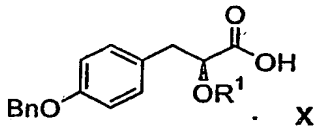
(iv). hydrolysing the crude compound of formula (9) obtained in step (iii) above in polar solvents using aqueous alkali to produce compound of formula (9a) acid



(9a)

wherein R^1 represents hydrogen or lower alkyl group,

(v). treating the compound of formula (9a) acid where R^1 represents hydrogen or lower alkyl group with chiral base in the presence of solvent to produce chemically and chirally pure (ee >99 %) salt of formula (16)

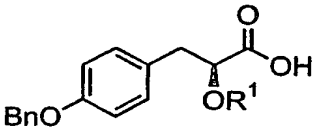


(16)

where R^1 represents hydrogen or lower alkyl group and X represents chiral bases such as R(+)-α-methylbenzylamine, S(+) phenylglycinol, cinchonidine, ephidrine, N-octylglucaramine or N-methylglucaramine,

(vi). if desired, recrystallising the compound of formula (16) obtained above in a solvent to produce highly pure compound of formula (16) where R^1 represents hydrogen or lower alkyl group,

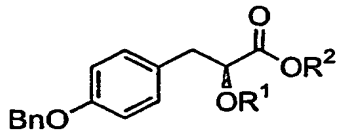
(vii). converting the compound of formula (16) defined above using a solvent and an acid to pure compound of formula (9a),



(9a)

where R^1 represents hydrogen or lower alkyl group,

(viii). esterifying the pure compound of formula (9a) defined above using alkylating agent in the presence of base or acid or acidic resin to produce pure compound of formula (9)



(9)

where R^1 represents hydrogen or lower alkyl group and R^2 represents lower alkyl group and

(ix). debenzylating the compound of formula (9) using solvents in the presence of metal catalysts to yield pure compound of formula (1) where R^1 represents hydrogen or lower alkyl group and R^2 represents lower alkyl group.

2. The process as claimed in claim 1, wherein the solvent used in step (i) is selected from aqueous methanol or ethanol.

3. The process as claimed in claims 1 and 2, wherein the diazotizing agent used in step (ii) is selected from sodium nitrite, isoamyl nitrite, potassium nitrite or ammonium nitrite.

4. The process as claimed in claims 1 to 3, wherein the acidic reagent used in step (ii) is selected from acids such as sulfuric acid, HCl or acetic acid.

5. The process as claimed in claims 1 to 4, wherein the organic solvent used in step (ii) is selected from $CHCl_3$, 1,4-dioxane, THF or acetone

6. The process as claimed in claims 1 to 5, wherein the alkylating agent used in step (iii) is selected from dimethyl sulfate, diethyl sulfate, methyliodide or ethyliodide.

7. The process as claimed in claims 1 to 6, wherein the solvent used in step (iii) is selected from toluene, benzene, DMF, DMSO or MIBK.

8. The process as claimed in claims 1 to 7, wherein the base used in step (iii) is selected from sodium carbonate, potassium carbonate, sodium methoxide or sodium hydride.

9. The process as claimed in claims 1 to 8, wherein the polar solvent used in step (iv) is selected from methanol, ethanol, propanol, isopropanol, acetone or methyl ethyl ketone.

10. The process as claimed in claims 1 to 9, wherein the alkali used in step (iv) is selected from sodium hydroxide or potassium hydroxide.

11. The process as claimed in claims 1 to 10, wherein the chiral base used in step (v) is selected from R(+)α-methylbenzylamine, S(+)-phenylglycinol, cinchonidine, ephidrine, N-octylglucaramine or N-methylglucaramine.

12. The process as claimed in claims 1 to 11, wherein the solvent used in step (v) is selected from methyl acetate, ethyl acetate, ethyl propanoate, n-butylacetate, methanol, ethanol, propanol, isopropanol, acetone, methyl isobutyl ketone or acetonitrile.

13. The process as claimed in claims 1 to 12, wherein the recrystallization in step (vi) is effected using solvent such as methyl acetate, ethyl acetate, ethyl propanoate, n-butylacetate, methanol, ethanol, propanol, isopropanol, acetone, methyl isobutyl ketone or acetonitrile.

14. The process as claimed in claims 1 to 13, wherein the acid used in step (vii) is selected from hydrochloric acid or sulfuric acid.

15. The process as claimed in claims 1 to 14, wherein the solvent used in step (vii) is selected from toluene, xylene, ethyl acetate, diethyl ether or methyl tertiary butyl ether.

16. The process as claimed in claims 1 to 15, wherein the alkylating agent used in step (viii) is selected from methanol, ethanol, propanol, isopropanol, butanol, dimethyl sulfate or diethyl sulfate.

17. The process as claimed in claims 1 to 16, wherein the acid used in step (viii) is selected from sulfuric acid or hydrochloric acid.

18. The process as claimed in claims 1 to 17, wherein the acidic resin used in step (viii) is selected from amberlite or amberlist.

19. The process as claimed in claims 1 to 18, wherein the base used in step (viii) is selected from potassium carbonate, sodium carbonate, sodium bicarbonate, potassium bicarbonate or organic bases such as alkoxides like sodium ethoxide, potassium tertiary butoxide or triethyl amine.

20. The process as claimed in claims 1 to 19, wherein the solvent used in step (ix) is selected from THF, aqueous acetic acid, ethyl acetate, aqueous or non aqueous (C_1-C_6) alcohols such as methanol, ethanol, propanol or isopropanol.

21. The process as claimed in claims 1 to 20, wherein the metal catalysts used in step (ix) is Pd/C.

22. An improved process for the preparation of 3-aryl-2-hydroxy propanoic acid derivatives of the formula (1) substantially as herein described with reference to the Examples.

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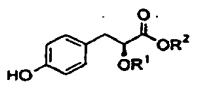
(54) Title: PROCESS FOR THE PREPARATION OF 3-ARYL-2-HYDROXY PROPANOIC ACID DERIVATIVES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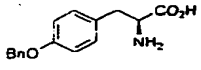
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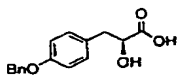
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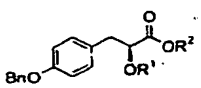
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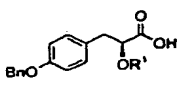
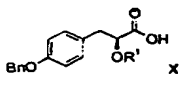

(9a)


(16)

(57) Abstract: The present invention relates to an improved process for the preparation of 3-aryl-2-hydroxy propanoic acid derivatives of formula (1) where R^1 represents hydrogen atom or (C_1-C_6)alkyl group and R^2 represents (C_1-C_6)alkyl group which comprises: (i) selectively benzylating L-tyrosine to yield compound of formula (15); (ii). diazotising the compound of formula (15) to produce compound of formula (8): (iii) simultaneous etherification and esterification of compound of formula (8) to obtain crude compound of formula (9) with ee>90 %: (iv) hydrolysing the crude compound of formula (9) to produce compound of formula (9a) acid; (v) treating the compound of formula (9a) with chiral base to produce pure salt of formula (16); (vi) converting the compound of formula (16) to pure compound of formula (9a): (vii) esterifying pure compound of formula (9a) to produce pure compound of formula (9); (viii) debenzylating the compound of formula (9) to yield pure compound of formula (1).

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INTERNATIONAL SEARCH REPORT

Ir ational Application No
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A. CLASSIFICATION OF SUBJECT MATTER
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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 00 26200 A (BATCHU CHANDRA SEKHAR ;CHEBIYYAM PRABHAKAR (IN); MAMILLAPALLY RAMA) 11 May 2000 (2000-05-11) cited in the application page 15, line 25 -page 17, line 8; figure 7 examples 12-14, 17-18 steps i-iv claims 47-51 example 1 steps iv-v	1-16, 19-22

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
11 April 2002	29/04/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Kardinal, S

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB 01/01699

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	HAIGH D ET AL: "NON-THIAZOLIDINEDIONE ANTIHYPERGLYCAEMIC AGENTS. PART 3: THE EFFECTS OF STEREOCHEMISTRY ON THE POTENCY OF ALPHA-METHOXY-BETA-PHENYLPROPAN OIC ACIDS" BIOORGANIC & MEDICINAL CHEMISTRY, ELSEVIER SCIENCE LTD, GB, vol. 7, 1999, pages 821-830, XP000995637 ISSN: 0968-0896 page 828 preparation of compound 5 -----	1-16, 19-22

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/IB 01/01699

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0026200 A	11-05-2000	AU 2953899 A	22-05-2000
		BR 9914438 A	26-06-2001
		CN 1323300 T	21-11-2001
		CZ 20010826 A3	15-08-2001
		EP 1124808 A1	22-08-2001
		WO 0026200 A1	11-05-2000
		NO 20011804 A	27-06-2001